II. The Rejections

A. The Rejection Under 35 U.S.C. § 103(a) Over Treco in View of DiMaio

On page 4 of the Office Action, claims 62–68 have been rejected under 35 U.S.C. 103(a) on the grounds that they are unpatentable over Treco, et al. (U.S. 5,641,670), herein "Treco," in view of DiMaio, et al. (WO 92/20784), herein "DiMaio." Applicants respectfully traverse the rejection.

On page 4 of the Office Action, Treco is relied upon for teaching vectors for protein production and delivery and a cell wherein the vector is integrated and wherein an endogenous gene is over-expressed by upregulation of the gene by a transcriptional regulatory sequence on the vector. DiMaio is relied upon for teaching a keratinocyte cell line transformed by HPV16 and expressing the E5 gene, disclosed as useful to identify compounds that inhibit the action of the E5 gene. Compounds are identified that affect the growth properties or biochemical characteristics of the cell line. See the paragraph spanning pages 4–5 of the Office Action.

The rationale for the rejection is found on page 5 of the Office Action. The Examiner asserts that it would have been obvious to use the Treco cells expressing EPO or any other activated endogenous gene to identify compounds that alter (1) the characteristics of the cell or (2) the biochemical properties of the activated protein. Applicants point out that to sustain the rejection, there must be motivation to use the cells to identify such compounds and a reasonable expectation that the cells could be successfully used to identify such compounds. In

the present case, for claims 62–68, the motivation was not present and, for claim 68, there was also no reasonable expectation of success.

Motivation To Identify Compounds That Alter Cellular Characteristics

The Examiner asserts that it would have been obvious to use the Treco cells to identify compounds that "alter characteristics of the cells." Accordingly, the Examiner must take the position that the person of ordinary skill in the art would have been motivated by the cited art to do this. Applicants respectfully disagree.

Treco fails to provide motivation to use the disclosed cells expressing the endogenous activated gene to identify compounds. Treco disclosed limited uses for cells expressing an activated endogenous gene. These limited uses are repeated throughout the extensive (66 pages) specification. These uses are always limited to the following: (1) using cells to produce a therapeutic protein for purification; (2) using cells to express a therapeutic protein *in vivo*; (3) using cells to produce an antigenic protein and produce antibodies *in vivo*; (4) using cells to produce agriculturally important proteins in animal, for example, bovine growth hormone in dairy production. For the Examiner's convenience, Applicants provide Exhibit A, which highlights all discussion regarding uses of the Treco cells.

None of these uses includes or suggests using the cells to identify a compound. Accordingly, Applicants respectfully submit that Treco fails to provide motivation to use the cells to identify a compound.

DiMaio is cited as a secondary reference. The Examiner relies on DiMaio as follows: "As taught by DiMaio, cell lines expressing a protein of interest were used for drug screening at the time of the invention." Applicants submit that this teaching is insufficient to motivate the person of ordinary skill in the art to use the Treco cells for compound screening.

A *prima facie* case of obviousness would require a teaching in DiMaio that compensates for the deficiencies of Treco, i.e., that specifically would motivate the person of ordinary skill in the art to use the Treco cells for compound screening. The stated teaching of DiMaio, relied upon by the Examiner, fails to provide this motivation. Accordingly, DiMaio fails to compensate for the deficiencies of Treco.

DiMaio addresses the role of the E5 gene in transformation by HPV16 and HPV18. The reference states that the invention is based on the discovery that the E5 gene can transform keratinocytes to tumorigenicity. See page 13. Against this backdrop, the reference discloses keratinocytes or epithelial cells expressing HPV16 or HPV18 E5 gene for identifying compounds that inhibit E5 action. The compounds are tested for the ability to affect cellular phenotypes that result from expression of E5, such as the ability to form tumors. The drug screening assay is summarized on page 6.

The cells made and used by DiMaio that express E5 and are used for screening are made by either inserting an expression vector or retrovirus encoding an exogenous E5 gene. Accordingly, there is no suggestion in DiMaio to perform the compound screening with a cell expressing an activated endogenous gene, i.e., the Treco cells.

Moreover, the E5 gene is a viral gene and, thus, not endogenous. As such it would not even be activated by the Treco methods. Therefore, DiMaio would not have used the Treco cells to express E5.

Because DiMaio taught only expression of an exogenous coding sequence, DiMaio would not have suggested compound screening against the Treco cells, which express endogenous activated genes. Accordingly, Applicants respectfully submit that the mere disclosure of screening against exogenous E5, without more, would not have motivated the person of ordinary skill in the art to screen against cell lines in which an endogenous gene is activated.

Motivation To Identify Compounds That Alter Biochemical Properties of The Protein Encoded

On page 5, the Examiner further bases the rejection on the position that it would have been obvious to use the Treco cells to identify compounds that alter the biochemical properties of the activated protein. Accordingly, the Examiner must take the position that there

was motivation to use the Treco cells to identify compounds that alter the biochemical properties of the activated protein. Applicants respectfully submit that Treco did not provide such motivation.

As discussed above, the uses disclosed by Treco were limited. None of these uses would have provided the motivation to use the cells to identify compounds that alter the biochemical properties of the activated protein. Thus, Treco fails to provide the requisite motivation.

The secondary reference, DiMaio, also fails to provide the motivation to use the Treco cells to identify compounds that alter the biochemical properties of the activated protein. As discussed above, DiMaio was limited to identifying compounds that affect cellular phenotypes induced by expression of an exogenous gene. This limited disclosure would not have motivated the person of ordinary skill in the art to screen against a protein expressed from an activated endogenous gene.

Motivation Based On Insufficient Target Protein Expression

On page 5 of the Office Action, the Examiner states that a motivation to use the Treco cells is that the Treco cells can "express endogenous genes that are usually silent or expressed at low levels," so that these cells "would have provided sufficient amount of protein to test the activity." The rationale appears to be the following: in the case where the target protein

is not naturally expressed at levels sufficient for compound screening, the person of ordinary skill in the art would have been motivated to use the Treco cells to express the target protein because the Treco cells could express the protein in sufficient amounts.

Applicants submit that a rejection on this basis is improper because this motivation is provided by the Examiner and not by the art.

Nothing in Treco addresses the issue of insufficient gene expression for compound screening. Nothing in DiMaio addresses this problem either. Even if this problem had been disclosed, the cited art still would not have motivated compound screening against a Treco cell. Treco does not disclose or suggest using the cells for compound screening and DiMaio shows that compound screening is adequately achieved by introducing an exogenous nucleic acid sequence on an expression vector. Thus, even if this problem had been disclosed, DiMaio provides a solution that would not have motivated the person of ordinary skill to solve the problem with the Treco cells.

Accordingly, there is nothing in the art to motivate replacing the cells taught by DiMaio, which achieved gene expression by an exogenous nucleic acid sequence with the Treco cells, that achieve gene expression by means of an activated endogenous nucleic acid sequence. For this reason alone the rejection is not legally sufficient.

The above argument notwithstanding, Applicants further point out that the Treco cells would have been disadvantageous for solving the (hypothetical) problem compared to cells containing an exogenous cloned sequence. The Examiner is directed to the attached Declaration, which discusses some of these disadvantages. The Declarant points out the adequacy of standard recombinant DNA approaches, taken by DiMaio, for drug screening at the time that the application was filed. He discusses how the Treco process is extremely burdensome compared to the standard recombinant approach used by DiMaio. He points out that the majority of recombination events are not productive for producing the desired gene, an issue which is also discussed by Treco. This is in contrast to the relatively high level of productive expression events obtained with standard recombinant approaches to protein expression. He concludes, therefore, that making and using the Treco cells would have imposed burdensome limitations on the drug screening process compared to the opportunities afforded by standard recombinant approaches for gene expression.

Applicants reiterate, however, that the problem disclosed by the Examiner, as providing the motivation to use the Treco cells for drug screening, is not suggested by either reference. Accordingly, the references, alone or in combination, do not provide the requisite motivation to support a *prima facie* case of obviousness. In fact, the disadvantages and limitations of the Treco methods would have guided the artisan away from the Treco method and, therefore, would have provided a negative motivation to use the Treco methods.

Motivation to Screen Non-Homologously Recombinant Cells

On page 5 of the Office Action, the Examiner discusses the rejection of claim 68. This claim is directed to a cell in which an endogenous gene is over-expressed by non-homologous recombination. The Examiner discusses Capecchi, but does not cite this reference to reject the claims, as the rejection is based only on Treco and DiMaio. The Examiner cites Capecchi to show that most of the insertion events in the Treco cells are random insertion events. Applicants point out, however, that Treco already provides this information. In column 21, lines 45–52, Treco indicates that homologous recombination events are far out-numbered by non-homologous recombination events. However, even if this is true, this would not have made the invention of claim 68 obvious.

First, Applicants have already established that it would not have been obvious to use the homologously recombinant cells of Treco for drug screening. However, even if it were to be established that it was obvious to use the homologously recombinant cells of Treco for drug screening, it still would not have been obvious to use the non-homologously recombinant cells of Treco for drug screening. Treco taught that non-homologous integration events would not activate the target gene. Therefore, there would have been no motivation to use such cells for drug screening and no reasonable expectation that such cells could be used successfully for drug screening.

On page 5 of the Office Action, the Examiner has taken the position that activation events will occur following non-homologous integration of the vector sequences. However, no evidence of activation was shown either by Treco or Capecchi. In fact, Treco actually taught that activation could not be achieved by non-homologous recombination. In column 36, lines 52–53, Treco states that cells, in which the transfecting DNA integrated randomly into the genome, could not produce the target gene (EPO). By disclosing that the target gene could not be activated by non-homologous recombination, Treco actually teaches away from using a non-homologously recombinant cell for drug screening.

Furthermore, this teaching also shows that the person of ordinary skill in the art would not have had a reasonable expectation of success. Because the reference teaches that the target gene could not be activated by non-homologous recombination, the person of ordinary skill in the art would not have reasonably expected that such activation would occur. In fact, that such events could be achieved was shown for the first time in Applicants' own disclosure.

Accordingly, the cited art, either alone or in combination, does not render claim 68 obvious. Moreover, the art actually teaches away from the invention of claim 68.

In view of the above discussion, Applicants submit that they have addressed each of the grounds of rejection and the rejection has been overcome. Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

The Rejection Under 35 U.S.C. § 103(a) Over Chappel In View of DiMaio

On page 2 of the Office Action, claims 62–67 have been rejected as being unpatentable over Chappel (U.S. 5,272,071; EP 0779362), herein "Chappel," in view of DiMaio, et al. (WO 92/20784), herein "DiMaio." Applicants respectfully traverse the rejection.

Chappel is relied upon for teaching a method of endogenous gene activation. It is further relied upon for teaching the expression of specific genes that are normally silent in a cell of choice. DiMaio is relied upon for exactly the same reasons as in the preceding rejection.

Applicants' arguments in response to the preceding rejection of claims 62–67 also apply to the present rejection. Applicants note, however, that Chappel does not disclose uses for cells expressing an activated gene. The reference is simply generically directed to activating an endogenous gene by homologous recombination. This is in distinction to Treco, which does disclose some specific uses. Nevertheless, no disclosure in Chappel would have suggested using these cells for drug screening. Other than this distinction, which does not affect Applicants' arguments, the arguments made in the preceding rejection apply exactly to the present rejection. Accordingly, these arguments need not be repeated, and the Examiner is referred to Applicants arguments above.

Accordingly, Applicants believe that they have addressed each of the grounds of the rejection and the rejection has been overcome. Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

Respectfully submitted,

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